

We claim:

- 1. A method for preventing cell death in a subject in need thereof comprising, administering to the subject an effective amount of a composition comprising a nucleic acid encoding at least one functional form of ATF6.**
- 2. The method according to claim 1, whereby the at least one functional form of ATF6 is chosen from a full-length form of ATF6, an N-terminal domain form of ATF6, a bZIP-ATF6 fragment, functional derivatives thereof, and combinations thereof.**
- 3. The method according to claim 2, whereby the full-length form of ATF6 is chosen from human ATF6- α , human ATF6- β , murine ATF6- α , and murine ATF6- β .**
- 4. The method according to claim 1, whereby the at least one functional form of ATF6 is a full-length form of ATF6 or an N-terminal domain form of ATF6 having at least one modification chosen from deletions, additions, amino acid substitutions, conservative amino acid substitutions, and combinations thereof.**
- 5. The method according to claim 1, whereby the nucleic acid further comprises a nucleic acid sequence encoding at least one basal transcription factor that binds to the ER-stress responsive element.**
- 6. The method according to claim 5, whereby the at least one basal transcription factor is chosen from NF-Y, YY1, functional derivatives thereof, and combinations thereof.**
- 7. The method according to claim 1, whereby the nucleic acid further comprises at least one transcriptional regulatory sequence.**

8. The method according to claim 7, whereby the at least one transcriptional regulatory sequence is chosen from promoters, enhancers, activators, terminators, polyadenylation signals, and combinations thereof.

9. The method according to claim 1, whereby the nucleic acid further comprises a nucleic acid sequence that induces expression of a functional form of ATF6.

10. The method according to claim 9, whereby the nucleic acid sequence that induces expression of a functional form of ATF6 is chosen from Irf1, presenilin 1, presenilin 2, transcription factors of ATF6, site-1 protease, site-2 protease, promoters that replace the original promoter of the gene encoding ATF6 in the cell's genome, enhancers that replace the original promoter of the gene encoding ATF6 in the cell's genome, and combinations thereof.

11. The method according to claim 1, whereby the administering is used as a stand-alone therapy.

12. The method according to claim 1, whereby the nucleic acid further comprises a vector chosen from viral vectors, plasmids, and cosmids.

13. The method according to claim 12, whereby the vector is a mammalian vector.

14. The method according to claim 12, whereby the vector directs nucleic acid delivery to the brain.

15. The method according to claim 12, whereby the vector is chosen from neural-specific expression vectors, blood brain barrier transmission-specific vectors, vectors comprising a neural-specific promoter, and combinations thereof.

16. The method according to claim 12, whereby the vector is chosen from retroviruses, adeno-associated viruses, herpes viruses, vaccinia viruses, RNA viruses, herpes simplex virus vectors, adenovirus vectors, adeno-associated virus vectors, lentivirus vectors, vectors comprising a platelet-derived growth factor promoter, vectors comprising a prion promoter, vectors comprising a neuron-specific enolase promoter, vectors comprising promoter/enhancer systems from an immediate early human cytomegalovirus, vectors comprising promoter/enhancer systems from a human neurofilament-light gene, vectors comprising terminators from a cytomegalovirus system, vectors comprising terminators from an SV40 system, and vectors comprising terminators from a bovine growth hormone polyadenylation sequence.

17. The method according to claim 1, whereby the composition further comprises at least one agent that enhances nucleic acid delivery to the brain.

18. The method according to claim 17, whereby the at least one agent that enhances nucleic acid delivery to the brain is mannitol.

19. The method according to claim 1, whereby the composition further comprises at least one pharmaceutically acceptable additive, lubricant, diluent, buffer, moistening agent, preservative agent, flavoring, adjuvant, carrier, stabilizer, suspending agent, emulsifying agent, propellant, or other vehicle.

20. A method for preventing cell death in a cell in need thereof comprising, administering to the cell an effective amount of a composition comprising a nucleic acid encoding at least one functional form of ATF6.

21. The method according to claim 20, whereby the at least one functional form of ATF6 is chosen from a full-length form of ATF6, an N-terminal domain form of ATF6, a bZIP-ATF6 fragment, functional derivatives thereof, and combinations thereof.

22. The method according to claim 21, whereby the full-length form of ATF6 is chosen from human ATF6- α , human ATF6- β , murine ATF6- α , and murine ATF6- β .

23. The method according to claim 20, whereby the at least one functional form of ATF6 is a full-length form of ATF6 or an N-terminal domain form of ATF6 having at least one modification chosen from deletions, additions, amino acid substitutions, conservative amino acid substitutions, and combinations thereof.

24. The method according to claim 20, whereby the nucleic acid further comprises a nucleic acid sequence encoding at least one basal transcription factor that binds to the ER-stress responsive element.

25. The method according to claim 24, whereby the at least one basal transcription factor is chosen from NF-Y, YY1, functional derivatives thereof, and combinations thereof.

26. The method according to claim 20, whereby the nucleic acid further comprises at least one transcriptional regulatory sequence.

27. The method according to claim 26, whereby the at least one transcriptional regulatory sequence is chosen from promoters, enhancers, activators, terminators, polyadenylation signals, and combinations thereof.

28. The method according to claim 20, whereby the nucleic acid further comprises a nucleic acid sequence that induces expression of a functional form of ATF6.

29. The method according to claim 28, whereby the nucleic acid sequence that induces expression of a functional form of ATF6 is chosen from Irf1, presenilin 1, presenilin 2, transcription factors of ATF6, site-1 protease, site-2 protease, promoters that replace the original promoter of the gene encoding ATF6 in the cell's genome, enhancers that replace the original promoter of the gene encoding ATF6 in the cell's genome, and combinations thereof.

30. The method according to claim 20, whereby the nucleic acid further comprises a vector chosen from viral vectors, plasmids, and cosmids.

31. The method according to claim 30, whereby the vector is a mammalian vector.

32. The method according to claim 30, whereby the vector is chosen from neural-specific expression vectors, blood brain barrier transmission-specific vectors, vectors comprising a neural-specific promoter, and combinations thereof.

33. The method according to claim 30, whereby the vector is chosen from retroviruses, adeno-associated viruses, herpes viruses, vaccinia viruses, RNA viruses, herpes simplex virus vectors, adenovirus vectors, adeno-associated virus vectors, lentivirus vectors, vectors comprising a platelet-derived growth factor promoter, vectors comprising a prion promoter, vectors comprising a neuron-specific enolase promoter, vectors comprising promoter/enhancer systems from an immediate early human cytomegalovirus,

vectors comprising promoter/enhancer systems from a human neurofilament-light gene, vectors comprising terminators from a cytomegalovirus system, vectors comprising terminators from an SV40 system, and vectors comprising terminators from a bovine growth hormone polyadenylation sequence.

34. The method according to claim 20, whereby the composition further comprises at least one pharmaceutically acceptable additive, lubricant, diluent, buffer, moistening agent, preservative agent, flavoring, adjuvant, carrier, stabilizer, suspending agent, emulsifying agent, propellant, or other vehicle.

35. A method for preventing cell death in a subject in need thereof comprising, administering to the subject an effective amount of a composition comprising at least one functional form of ATF6.

36. The method according to claim 35, whereby the at least one functional form of ATF6 is chosen from a full-length form of ATF6, an N-terminal domain form of ATF6, a bZIP-ATF6 fragment functional, derivatives thereof, and combinations thereof.

37. The method according to claim 36, whereby the full-length functional form is chosen from human ATF6- α , human ATF6- β , murine ATF6- α , and murine ATF6- β .

38. The method according to claim 35, whereby the at least one functional form of ATF6 is a full-length form of ATF6 or an N-terminal domain form of ATF6 having at least one modification chosen from deletions, additions, amino acid substitutions, conservative amino acid substitutions, and combinations thereof.

39. The method according to claim 35, whereby the at least one functional form of ATF6 comprises at least one covalent modification.

40. The method according to claim 39, whereby the at least one modification occurs in at least one region chosen from the peptide backbone, the amino acid side-chains, the amino terminus and the carboxyl terminus.

41. The method according to claim 39, whereby the at least one modification is chosen from acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of a functional moiety, covalent attachment of a lipid, covalent attachment of a lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formylation, gamma-carboxylation, glycosylation, glycoposphatidylinositol anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins, arginylation, and ubiquitination.

42. The method according to claim 35, whereby the administering is used as a stand-alone therapy.

43. The method according to claim 35, whereby the composition further comprises at least one pharmaceutically acceptable additive, lubricant, diluent, buffer, moistening agent, preservative agent, flavoring, adjuvant, carrier, stabilizer, suspending agent, emulsifying agent, propellant, or other vehicle.

44. A method for preventing cell death in a cell in need thereof comprising administering to the cell an effective amount of a composition comprising at least one functional form of ATF6.

45. The method according to claim 44, whereby the at least one functional form of ATF6 is chosen from a full-length form of ATF6, an N-terminal domain form of ATF6, a bZIP-ATF6 fragment, functional derivatives thereof, and combinations thereof.

46. The method according to claim 45, whereby the full-length functional form is chosen from human ATF6- α , human ATF6- β , murine ATF6- α , and murine ATF6- β .

47. The method according to claim 44, whereby the at least one functional form of ATF6 is a full-length form of ATF6 or an N-terminal domain form of ATF6 having at least one modification chosen from deletions, additions, amino acid substitutions, conservative amino acid substitutions, and combinations thereof.

48. The method according to claim 44, whereby the at least one functional form of ATF6 comprises at least one covalent modification.

49. The method according to claim 48, whereby the at least one modification occurs in at least one region chosen from the peptide backbone, the amino acid side-chains, the amino terminus and the carboxyl terminus.

50. The method according to claim 48, whereby the at least one modification is a from acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of other functional moiety, covalent attachment of a lipid, covalent attachment of a lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation,

demethylation, formation of covalent cross-links, formylation, gamma-carboxylation, glycosylation, glycoposphatidylinositol anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins, arginylation, and ubiquitination.

51. The method according to claim 44, whereby the composition further comprises at least one pharmaceutically acceptable additive, lubricant, diluent, buffer, moistening agent, preservative agent, flavoring, adjuvant, carrier, stabilizer, suspending agent, emulsifying agent, propellant, or other vehicle.

52. A method for preventing cell death in a subject in need thereof comprising, administering to the subject a treatment whereby said treatment induces or suppresses expression of a functional form of ATF6 in an effective amount in the subject.

53. The method according to claim 52, whereby the treatment induces expression a functional form of ATF6.

54. The method according to claim 52, whereby the treatment induces overexpression of a functional form of ATF6.

55. The method according to claim 52, whereby the treatment comprises administering a composition chosen from at least one nucleic acid and at least one protein.

56. The method according to claim 52, whereby the treatment induces expression or overexpression of a functional form of ATF6 by inducing the Unfolded Protein Response.

57. The method according to claim 55, whereby the nucleic acid encodes at least one basal transcription factor that binds to the ER-stress responsive element.

58. The method according to claim 57, whereby the at least one basal transcription factor is chosen from NF-Y, YY1, functional derivatives thereof, and combinations thereof.

59. The method according to claim 55, whereby the nucleic acid comprises at least one transcriptional regulatory sequence.

60. The method according to claim 59, whereby the at least one transcriptional regulatory sequence is chosen from promoters, enhancers, activators, terminators, polyadenylation signals, and combinations thereof.

61. The method according to claim 55, whereby the nucleic acid induces expression of a functional form of ATF6.

62. The method according to claim 61, whereby the nucleic acid sequence that induces expression of a functional form of ATF6 is chosen from Ire1, presenilin 1, preselinin 2, transcription factors of ATF6, site-1 protease, site-2 protease, promoters that replace the original promoter of the gene encoding ATF6 in the cell's genome, enhancers that replace the original promoter of the gene encoding ATF6 in the cell's genome, and combinations thereof.

63. The method according to claim 52, whereby the administering is used as a stand-alone therapy.

64. The method according to claim 55, whereby the nucleic acid comprises a vector chosen from viral vectors, plasmids, and cosmids.

65. The method according to claim 64, whereby the vector is a mammalian vector.

66. The method according to claim 64, whereby the vector directs nucleic acid delivery to the brain.

67. The method according to claim 64, whereby the vector is chosen from neural-specific expression vectors, blood brain barrier transmission-specific vectors, vectors comprising a neural-specific promoter, and combinations thereof.

68. The method according to claim 64, whereby the vector is chosen from retroviruses, adeno-associated viruses, herpes viruses, vaccinia viruses, RNA viruses, herpes simplex virus vectors, adenovirus vectors, adeno-associated virus vectors, lentivirus vectors, vectors comprising a platelet-derived growth factor promoter, vectors comprising a prion promoter, vectors comprising a neuron-specific enolase promoter, vectors comprising promoter/enhancer systems from an immediate early human cytomegalovirus, vectors comprising promoter/enhancer systems from a human neurofilament-light gene, vectors comprising terminators from a cytomegalovirus system, vectors comprising terminators from an SV40 system, and vectors comprising terminators from a bovine growth hormone polyadenylation sequence.

69. The method according to claim 52, whereby the composition further comprises at least one agent that enhances nucleic acid delivery to the brain.

70. The method according to claim 69, whereby the at least one agent that enhances nucleic acid delivery to the brain is mannitol.

71. The method according to claim 52, whereby the composition further comprises at least one pharmaceutically acceptable additive, lubricant, diluent, buffer, moistening agent, preservative agent, flavoring, adjuvant, carrier, stabilizer, suspending agent, emulsifying agent, propellant, or other vehicle.

72. A method for preventing cell death in a cell in need thereof comprising, administering to the subject a treatment whereby said treatment induces or suppresses expression of a functional form of ATF6 in an effective amount in the cell.

73. The method according to claim 72, whereby the treatment induces expression a functional form of ATF6.

74. The method according to claim 72, whereby the treatment induces overexpression of a functional form of ATF6.

75. The method according to claim 72, whereby the treatment comprises administering a composition chosen from at least one nucleic acid and at least one protein.

76. The method according to claim 72, whereby the treatment induces expression or overexpression of a functional form of ATF6 by inducing the Unfolded Protein Response.

77. The method according to claim 75, whereby the nucleic acid encodes at least one basal transcription factor that binds to the ER-stress responsive element.

78. The method according to claim 77, whereby the at least one basal transcription factor is chosen from NF-Y, YY1, functional derivatives thereof, and combinations thereof.

79. The method according to claim 75, whereby the nucleic acid comprises at least one transcriptional regulatory sequence.

80. The method according to claim 79, whereby the at least one transcriptional regulatory sequence is chosen from promoters, enhancers, activators, terminators, polyadenylation signals, and combinations thereof.

81. The method according to claim 75, whereby the nucleic acid comprises a nucleic acid sequence that induces expression of a functional form of ATF6.

82. The method according to claim 81, whereby the nucleic acid sequence that induces expression of a functional form of ATF6 is chosen from Irf1, presenilin 1, preselinin 2, transcription factors of ATF6, site-1 protease, site-2 protease, promoters that replace the original promoter of the gene encoding ATF6 in the cell's genome, enhancers that replace the original promoter of the gene encoding ATF6 in the cell's genome, and combinations thereof.

83. The method according to claim 75, whereby the nucleic acid comprises a vector chosen from viral vectors, plasmids, and cosmids.

84. The method according to claim 83, whereby the vector is a mammalian vector.

85. The method according to claim 83, whereby the vector is chosen from neural-specific expression vectors, blood brain barrier transmission-specific vectors, vectors comprising a neural-specific promoter, and combinations thereof.

86. The method according to claim 83, whereby the vector is chosen from retroviruses, adeno-associated viruses, herpes viruses, vaccinia viruses,

RNA viruses, herpes simplex virus vectors, adenovirus vectors, adeno-associated virus vectors, lentivirus vectors, vectors comprising a platelet-derived growth factor promoter, vectors comprising a prion promoter, vectors comprising a neuron-specific enolase promoter, vectors comprising promoter/enhancer systems from an immediate early human cytomegalovirus, vectors comprising promoter/enhancer systems from a human neurofilament-light gene, vectors comprising terminators from a cytomegalovirus system, vectors comprising terminators from an SV40 system, and vectors comprising terminators from a bovine growth hormone polyadenylation sequence.

87. The method according to claim 72, whereby the composition further comprises at least one pharmaceutically acceptable additive, lubricant, diluent, buffer, moistening agent, preservative agent, flavoring, adjuvant, carrier, stabilizer, suspending agent, emulsifying agent, propellant, or other vehicle.

88. A composition comprising at least one viral vector wherein the at least one viral vector comprises nucleic acid encoding a functional form of ATF6.

89. The composition according to claim 88, wherein the at least one functional form of ATF6 is chosen from a full-length form of ATF6, an N-terminal domain form of ATF6, a bZIP-ATF6 fragment, functional derivatives thereof, and combinations thereof.

90. The composition according to claim 89, wherein the full-length form of ATF6 is chosen from human ATF6- α , human ATF6- β , murine ATF6- α , and murine ATF6- β .

91. The composition according to claim 88, wherein the at least one functional form of ATF6 is a full-length form of ATF6 or an N-terminal domain form of ATF6 having at least one modification chosen from deletions, additions, amino acid substitutions, conservative amino acid substitutions, and combinations thereof.

92. The composition according to claim 88, wherein the nucleic acid further comprises a nucleic acid sequence encoding at least one basal transcription factor that binds to the ER-stress responsive element.

93. The composition according to claim 92, wherein the at least one basal transcription factor is chosen from NF-Y, YY1, functional derivatives thereof, and combinations thereof.

94. The composition according to claim 88, wherein the nucleic acid further comprises at least one transcriptional regulatory sequence.

95. The composition according to claim 94, wherein the at least one transcriptional regulatory sequence is chosen from promoters, enhancers, activators, terminators, polyadenylation signals, and combinations thereof.

96. The composition according to claim 88, wherein the nucleic acid further comprises a nucleic acid sequence that induces expression of a functional form of ATF6.

97. The composition according to claim 96, wherein the nucleic acid sequence that induces expression of a functional form of ATF6 is chosen from Ire1, presenilin 1, preselinin 2, transcription factors of ATF6, site-1 protease, site-2 protease, promoters that replace the original promoter of the gene encoding ATF6 in the cell's genome, enhancers that replace the original

promoter of the gene encoding ATF6 in the cell's genome, and combinations thereof.

98. The composition according to claim 88, wherein the at least one viral vector is chosen from neural-specific expression vectors, blood brain barrier transmission-specific vectors, vectors comprising a neural-specific promoter, and combinations thereof.

99. The composition according to claim 88, wherein the at least one viral vector is chosen from retroviruses, adeno-associated viruses, herpes viruses, vaccinia viruses, and RNA viruses.

100. The composition according to claim 88, wherein the at least one viral vector directs nucleic acid delivery to the brain.

101. The composition according to claim 88, wherein the at least one viral vector is chosen from neural-specific expression vectors, blood brain barrier transmission-specific vectors, vectors comprising a neural-specific promoter, and combinations thereof.

102. The composition according to claim 88, wherein the at least one viral vector chosen is from retroviruses, adeno-associated viruses, herpes viruses, vaccinia viruses, RNA viruses, herpes simplex virus vectors, adenovirus vectors, adeno-associated virus vectors, lentivirus vectors, vectors comprising a platelet-derived growth factor promoter, vectors comprising a prion promoter, vectors comprising a neuron-specific enolase promoter, vectors comprising promoter/enhancer systems from an immediate early human cytomegalovirus, vectors comprising promoter/enhancer systems from a human neurofilament-light gene, vectors comprising terminators from a cytomegalovirus system, vectors comprising terminators from an SV40

system, and vectors comprising terminators from a bovine growth hormone polyadenylation sequence.

103. The composition according to claim 88, wherein the composition further comprises at least one agent that enhances nucleic acid delivery to the brain.

104. The composition according to claim 103, whereby the at least one agent that enhances nucleic acid delivery to the brain is mannitol.

105. The composition according to claim 88, wherein the composition further comprises at least one pharmaceutically acceptable additive, lubricant, diluent, buffer, moistening agent, preservative agent, flavoring, adjuvant, carrier, stabilizer, suspending agent, emulsifying agent, propellant, or other vehicle.

106. A method for determining whether a substance increases or decreases the activity of at least one functional form of ATF6 in a cell whose production by a cell evokes a responsive change in at least one characteristic, comprising:

- providing a first cell line which produces at least one functional form of ATF6;

- providing a second cell line which produces the at least one functional form of ATF6 at a lower level than the first cell line, or does not produce the at least one functional form of ATF6 at all;

- contacting the substance with the first and second cell lines;

and

- comparing the at least one characteristic of the first cell lines with the second cell lines.

107. The method according to claim 106, whereby the at least one functional form of ATF6 is chosen from an endogenous form of ATF6, a full-length form of ATF6, an N-terminal domain form of ATF6, a bZIP-ATF6 fragment, functional derivatives thereof, and combinations thereof.

108. The method according to claim 106, whereby the first and second cell lines are neurons.

109. The method according to claim 106, whereby first and second cell lines are nigral neurons.

110. The method according to claim 106, whereby the at least one characteristic is chosen from a characteristic that is observable with the naked eye, a characteristic that is a cultural characteristic of the cell, a characteristic that is a morphological characteristic, and combinations thereof.

111. The method according to claim 106, whereby the at least one characteristic is a measure of an amount of ATF6 mRNA.

112. The method according to claim 106, whereby the at least one characteristic is a measure of an amount of at least one functional form of ATF6.

113. The method according to claim 106, whereby the at least one characteristic is chosen from a rate of cell death, a rate of cell proliferation, and combinations thereof.

114. The method according to claim 106, whereby the at least one characteristic is a response along the UPR signaling pathway.

115. The method according to claim 106, whereby the at least one characteristic is an expression of a gene chosen from Ire1, presenilin 1, presenilin 2, ATF6 regulated genes, and combination thereof.

116. The method according to claim 106, whereby the at least one characteristic is an expression of a UDR-regulated gene.

117. The method according to claim 116, whereby the UDR-regulated gene is chosen from a molecular chaperone BiP gene, a gene involved in protein glycosylation, a gene involved in protein secretion, a gene involved in protein degradation, a gene involved in membrane biosynthesis, and combinations thereof,

118. The method according to claim 106, whereby the at least one characteristic is a cleavage rate of a full length ATF6.

119. The method according to claim 106, whereby the at least one characteristic is a rate of protein folding.

120. The method according to claim 106, whereby the at least one characteristic is a measure of an amount of protein accumulation.

121. The method according to claim 106, whereby the at least one characteristic is chosen from a measure of an amount of protein aggregation, a measure of an amount of protein precipitation, a measure of an amount of protein plaques, and combinations thereof.